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09/393,579	09/09/1999	STEVE DE KECZER	IR98-7410	2931

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EXAMINER	
CELSA, BENNETT M	
ART UNIT	**PAPER NUMBER**
1627	10

DATE MAILED: 12/31/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

file copy

Office Action Summary

Application No.	Applicant(s)
09/393,579	De Keczer et al.
Examiner	**Art Unit**
Bennett Celsa	1627

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 2, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-45 and 47-56* is/are pending in the application.

4a) Of the above, claim(s) *2-13, 17, 18, 20, 31, 34-36, 45, and 47-56* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 14-16, 19, 21-30, 32, 33, and 37-44* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Response to Amendment

Applicant's amendment dated 10/2/01 in paper no. 9 is hereby acknowledged.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

Claims 1-45 and 47-56 are currently pending.

Claims 2-13, 17-18, 20, 31, 34-36, 45 and 47-56 are withdrawn from further consideration.

Claims 1, 14-16, 19, 21-30, 32, 33 and 37-44 are under consideration. .

Election/Restriction

2. Applicant's election without traverse of Group III (claims 14-16, 19-30, 32-44 and 46) in Paper No. 5 is again acknowledged.

3. Applicant's further election of species , in Paper No.5 of :

a. *α-bromoacetylbenzoic acid (BABA) as the "protected alkylating agent".*

b. phosphine as the "disulfide reducing agent";

c. alkaline phosphatase as the "activating agent capable of deprotecting to the protected alkylating agent"; and

d. an antibody as the "reagent capable of specifically binding to modified homocysteine", is acknowledged, which reads on claims 1, 14-16, 19, 21-30, 32, 33, 37-44 and 46. Because

applicant did not distinctly and specifically point out the supposed errors in the election of species requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)) . It is noted that the sake of expediency and compact prosecution, claim 1 was included in the elected invention since claim 14 is dependent thereon.

4. This application contains claims 2-13, 17-18, 20, 31, 34-36, 45 and 47-56 drawn to a nonelected invention. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Withdrawn *Objection (s) and/or Rejection (s)*

Applicant's amendment has overcome the indefinite rejection of claims 32 and 44 w/r to the terms "ligand" and "receptor".

Applicant's amendment has overcome the indefinite rejection of claims 1, 15 and 16 for lack of antecedent basis for the term "The reagent"

The indefinite rejections relating to claim 46 are rendered moot by applicant's amendment canceling this claim.

New Objection (s) and/or Rejection (s)

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 14-16, 19, 21-30, 32, 33 and 37-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (NEW MATTER REJECTION).

Applicant's amendment referring to protection and deprotection language (e.g. claim 1 and other independent claims) which was not present in the specification or original claims and to which no specification support was pointed to constitutes new matter. Additionally, amending (e.g. claims 19 and other independant claims) to include modification beyond "conjugation" with homocystein constitutes new matter. Applicant must cancel the new matter in response to this rejection.

7. Claims 19, 21-30, 32, 33 and 37-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The term *"capable of reacting* with a functional nucleophilic group" and "*unreactive* to a nucleophilic group" in the independent claims claim are relative terms which renders the claim

indefinite. These terms are not defined by the claim; nor does the specification provide a standard for ascertaining the requisite degree of "reactive capability" or "unreactivity" nor the conditions (e.g. reactive with what and under what conditions) for evaluationg such degree of reactivity; and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Outstanding Objection (s) and/or Rejection (s)

8. Claims 1, 15,16,19, 32 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

B. claims 1, 19, 32 and 44, "a protected alkylating agent" is indefinite as to what portion of the "alkylating agent" (e.g. amino, sulfhydryl, carboxyl etc) is being protected and from what chemical conditions and/or reaction protection is being sought.

D. In claims 19, 32 and 44, "chemically modifying homocysteine" or "homocysteine is modified by a reagent" lacks metes and bounds regarding the type of homocysteine modifications within the scope of the claim and the resulting homocysteine structure.

Discussion

Applicant's arguments directed to the above indefinite rejections were considered but deemed nonpersuasive for the following reasons.

Regarding item B. above applicant argues that "protecting" is clearly defined by the specification and cites page 17 (lines 15-25) and page 19 (lines 20-25). Applicant's argument is misguided.

The specification on page 17 defines a markush listing of "alkylating agents" (e.g. alpha haloaldehydes etc) and page 19 merely states that "Protected alkylating reagents useful for coupling two molecules in aqueous solution must have a group suitable for conjugating the reagent to one of the molecules of interest" which must have a "nucleophilic group" which permits coupling.

Thus, the purported specification "definition" encompasses any alpha haloketone or alpha haloaldehyde (e.g. as recited on page 17) which has a "group suitable for conjugating" and would include the elected species (e.g. BABA) which has a functional group suitable for conjugating with a nucleophile.

Additionally, neither the claims (as amended) nor the specification portion pointed to by applicant address the above indefinite issue e.g. what portion of the "alkylating agent" (e.g. amino, sulfhydryl, carboxyl etc) is being protected and from what chemical conditions and/or reaction protection is being sought.

Applicant's further argument(and amended claims) that a "protected alkylating agent" be defined as having "a protected functional group that when unprotected would react with a nucleophilic group" fails to address the issue of the indefinite rejection as defined above.

Turning to item d. above applicant argues that amending to recite that the unprotected functional group present in the alkylating reagent reacts with homocysteine renders definite the metes and bound of the present claims. The Examiner respectfully disagrees.

The rectiation that a "functional group" "reacts" with a "nucleophilic group" present in homocysteine fails to address the type of homocysteine modifications within the scope of the claim and the resulting homocysteine structure; since the claim fails to recite the structure of the functional group; how and where it attaches to homocysteine; nor the type of reaction which occurs with the nucleophilic group of homocysteine.

Accordingly, for the reasons recited above, the indefinite rejection is hereby retained.

9. Claims 1 and 14 are rejected under 35 U.S.C. 102(b,e) as being anticipated by Metzger et al. US Pat. No. 5,700,910 (12/97)..

Metzger et al. disclose a composition comprising a "disulfide reducing agent" (e.g. Zn in HCL/H2SO4: see col. 2, lin 41) and a "protected alkylating agent" of formula III (e.g. see col. 2, line 45) which anticipates the presently claimed invention.

It is noted that intended use limitations are not given patentable weight and compound structure within the present claim scope must inherently possess functionally claimed characteristics (E.g. "deprotection of said reagent is catalyzed by an enzyme").

In any event, the Metzger formula III composition would be within the scope of the presently claimed invention as amended, since the formula III compound

a. meets the specification requirement (e.g. that the formula III compound has a functional group suitable for conjugating with a nucleophile as described on present specification page 19) and is intended to be used as an "alkylating agent"and thus constitutes a "protected alkylating agent" within the scope of the presently claimed invention; and/or

b. the formula III compounds intended alkylating agent use is realized upon being reacted with a nucleophilic group upon being "deprotected" [e.g. placed in the presence of a disulfide containing compound (e.g. Metzger formula II compound) and/or a disulfide reducing agent (e.g. Zn in HCL/H2SO4)].

Discussion

Applicant's arguments directed to the above anticipation rejection over the Metzger reference were considered but deemed nonpersuasive for the following reasons. Initially, it is noted that the above rejection was modifed in order to address applicant's newly amended claim language.

Applicant argues that the Metzger formula III compound does not contain a "protected functional group".

This argument was considered but not deemed persuasive since the Metzger formula III compound meets the present specification's requirement for a "protected alkylating agent" and additionally the Metzger formula compound contains chemical structure that satisfies applicant's

claimed function e.g. the Metzger formula III compound is an "alkylating agent" which is capable of performing applicant's intended function (e.g. alkylation) when placed in the presence of a nucleophile under "deprotecting conditions" (e.g. presence of the disulfide compound and/or reducing agent).

Accordingly, the above anticipation rejection, as modified in response to applicant's amended invention, is hereby maintained..

10. Claims 1, 14-16, 19, 21-30, 32, 33 and 37-44 are rejected under 35 U.S.C. 102(b) as being anticipated or in the alternative as being obvious over Van Atta et al. US Pat. No. 5,478,729 (12/95)..

Van Atta et al. disclose compositions, kits and assays for performing immunodetection of homocysteine in a sample. (E.g. see abstract; patent claims). The assays can be performed homogeneously or heterogeneously using solid supports (e.g. beads such as glass beads; see col. 5). The use of "modifying reagents" especially "alkylating agents" which are preferred and most preferentially the use of α-bromoacetylbenzoic acid (BABA) as the "protected alkylating agent" is specifically disclosed, exemplified and claimed (e.g. see col. 9, lines 20-25; patent claims 10, 25 etc.. It is noted that both BABA (e.g. example IV) and modified BABA (e.g. BABA-N-hydroxysuccinamide ester: see col. 21) constitute "protected alkylating agents" which are within the scope of the presently claimed invention. It is further noted that if a compound is clearly within the scope of the presently claimed invention; claimed functional characteristic must

inherently flow therefrom (e.g. "deprotection" and reaction with a nucleophile). Both BABA and BABA-N-hydroxysuccinamide ester meet the specification requirement (e.g. has a functional group suitable for conjugating with a nucleophile as described on present specification page 19) and is intended to be used (and indeed is used) as an "alkylating agent"and thus constitutes a "protected alkylating agent" within the scope of the presently claimed invention; and/or both BABA and BABA-N-hydroxysuccinamide ester react with a nucleophilic group upon being "deprotected" [e.g. placed in the presence of a disulfide containing compound and/or disulfide reducing agent].

Additionally the patent discloses "releasing agents" particularly "disulfide reducing agents" with disclosed and exemplified phosphines being most preferred (e.g. see col. 15; Example IV and TCEP).

Accordingly, the reference clearly anticipates claims 1 and 14-16 which merely require a "protected alkylating agent alone or further combined with a "disulfide reducing agent" (e.g. TCEP).

With regard to present claims 32 and 33 which recite a homocysteine assay requiring a sample to be contacted with "a protected alkylating reagent" and a "ligand" that is capable of "specifically binding to a "modified homocysteine" to form an immunocomplex and further comprising a disulfide reducing agent; it is initially noted that if "ligand" is interpreted as being an antibody, the reference, as discussed above would anticipate claims 32 and 33. It is further noted

that the reference specifically teaches the incorporation of a "ligand" as part of the "modifying agent" (e.g. see col. 14 bottom) which would alternatively anticipate this claim language.

To the extent that the presently claimed inventions are drawn to kits in which the individual components are separate or combined it is noted that the reference specifically is addressed to kits (E.g. see col. 20; patent claims 27-27). To the extent that the kit claims and/or methods further require the presence of an "activating agent capable of deprotecting to the protected alkylating agent" (e.g. alkaline phosphatase) it is noted that the patent reference teaches the use of "alkaline phosphatase" (e.g. Hcy-ABA-AP) in generating antibodies (e.g. see col. 21; and bottom of col. 22-top of col. 23) and thus would anticipate or render obvious the presence of alkaline phosphatase in kit form (e.g. claims 19, 26). With regard to the presence of "alkaline phosphatase" as part of the immunological assay per se it is noted that the use of "enzymes such as alkaline phosphatase" as a preferred "label" (e.g. see col. 5, lines 30-40) and the use of these enzymes (e.g G-6Ph dehydrogenase) in the liquid assay (e.g. see bottom of col. 18-top of col. 19) would either anticipate or render obvious the incorporation of alkaline phosphatase in solution with the protecting alkylating agent, antibody etc. as found in the presently claimed invention. The use of microtiter well plates are disclosed (E.g. see col. 24, line 44).

Discussion

Applicant's arguments directed to the above anticipation rejection over the Van Atta et al. reference was considered but is deemed nonpersuasive for the following reasons. Initially, it is noted that the above rejection was modifed in order to address applicant's newly amended claim language.

Applicant argues that neither BABA nor BABA-N-hydroxysuccinamide ester are "protected alkylating agents" within the scope of the presently claimed invention since neither compound has a "protected functional group" that is only reactive with a nucleophile upon deprotection. Applicant's argument is not found persuasive for the following reasons.

Applicant's is not consistent with the specification which describes "alkylating agents" and "protected alkylating agents" which clearly encompass applicant's elected species (e.g. BABA) as well as the BABA-N-hydroxysuccinamide ester reference compound since both reference compounds are clearly within the scope of " protected alkylating agents" (e.g. see specificaiton pages 17 and 19) since they are alkylating agents which have a "suitable group for conjugating" another molecules "nucleophilic group" under the requisite reaction conditions.

Accordingly, for the reasons recited above and for the reasons recited in the revised anticipation rejection, the above anticipation rejection is hereby maintained.

Double Patenting

11. Claims 1, 14-16, 19, 21-30, 32, 33 and 37-44 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 5,478,729.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent claims disclose, compositions, kits and methods of use thereof comprising "modifying agents" particularly alkylating agents (e.g ketones substituted at alpha position by halogens) , releasing agent (e.g. reducing agents), antibodies and labels which can be selected from 5 different types one of which are enzymes (e.g. see patent claim 13) in solution with or without supports. In this regard, BABA as being the ketone substituted at the alpha position by halogen; phosphines as disulfide reducing agents; and alkaline phosphatase for use in kits and assays are either disclosed or specifically exemplified as being preferred embodiments (e.g. see examples; bottom of col 15, col. 19 ; bottom of col. 20 to top of col. 21; col. 13, lines 25-30; col 5. Accordingly, the patent claim reference would render obvious the presently claimed invention.

Regarding the newly amended claim limitations describing a "protected alkylating agent" is is noted that if a compound is clearly within the scope of the presently claimed invention; claimed functional characteristic must inherently flow therefrom (e.g. "deprotection" and subsequent reaction with a nucleophile). BABA meets the specification requirement for a "protected alkylating agent" (e.g. has a functional group suitable for conjugating with a

nucleophile as described on present specification page 19) and is intended to be used (and indeed is used) as an "alkylating agent"and thus constitutes a "protected alkylating agent" within the scope of the presently claimed invention; and/or BABA reacts with a nucleophilic group upon being "deprotected" [e.g. placed in the presence of a disulfide containing compound and/or disulfide reducing agent].

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat (art unit 1627), can be reached at (703)308-0570.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1627)

December 28, 2001

BENNETT CELSA
PRIMARY EXAMINER